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Effects of Cognitive Reserve on Cognition in Individuals With Central Nervous System Disease

Varna R. Jammula, BS, Heather Leeper, MD,* Mark R. Gilbert, MD,* Diane Cooper, MS,† and Terri S. Armstrong, PhD**

Abstract: Cognitive reserve (CR) has been proposed to account for functional outcome differences in brain pathology and its clinical manifestations. The purpose of our paper is to systematically review the effects of CR on cognitive outcomes in individuals with neurodegenerative and structural CNS diseases. We performed a systematic search of PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsychInfo using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Seventeen studies met the predetermined inclusion criteria and were selected for review. Education level was the most commonly used measure for CR, and various neuropsychological tests were used to measure cognitive outcomes. Regardless of the CNS disease of the individuals, almost all of the studies reported a positive association between CR and cognitive outcomes when they were evaluated cross-sectionally. However, when evaluated longitudinally, CR had either no effect on, or a negative association with, cognitive outcomes. Based on studies across a broad spectrum of CNS diseases, our findings suggest that CR may serve as a predictor of cognitive outcomes in individuals with CNS diseases. However, studies to date are limited by a lack of imaging analyses and standardized assessment strategies. The ability to use a standardized measure to assess the longitudinal effects of CR may allow for the development of more targeted treatment methods, resulting in improved disease outcomes for individuals.

Key Words: cognitive reserve, cognition, central nervous system disease, brain injury

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From the *Neuro-Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and †NIH Library/Office of Research Services, National Institutes of Health, Bethesda, Maryland.

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Correspondence: Varna R. Jammula, BS, Neuro-Oncology Branch, National Cancer Institute, National Institutes of Health, 9030 Old Georgetown Road, Room 214, Bethesda, Maryland 20814 (email: jammulavr@nih.gov).

AD = Alzheimer disease. **BR** = brain reserve. **CR** = cognitive reserve. **PD** = Parkinson disease. **TBI** = traumatic brain injury.

Several studies have suggested that individuals' degree of brain damage and their clinical outcomes may not have a direct relationship with neurodegenerative (Katzman et al, 1988; Stern, 2002) and structural brain diseases (Lingsma et al, 2010). Cognitive reserve (CR) refers to how the brain accounts for outcome differences in brain pathology and its clinical manifestations (Stern, 2002). There are two related hypotheses that explain the relationship between CR and clinical outcomes throughout the course of a disease. In the active model, CR is hypothesized to be a protective factor in disease pathology by using existing neural networks more efficiently to compensate for brain damage. In the passive model, CR is hypothesized to describe the relationship between CR and the amount of damage that can be sustained by the brain before showing clinical signs of a disease (Stern, 2002).

CR is split into two main features known as CR and brain reserve (BR) (Christensen et al, 2008; Stern, 2002). Whereas CR is a qualitative measure of brain function manifested by education level, IQ, and occupational attainment, BR is a quantitative measure of brain size, structures, and synapses (Christensen et al, 2008; Tucker and Stern, 2011). Individual differences in these measures may explain one's susceptibility to adverse clinical outcomes that are commonly seen with brain damage or disease progression. Individuals with a higher CR and/or BR are believed to have a brain that can sustain more injury compared with individuals with a lower CR and/or BR (Satz, 1993; Stern, 2002, 2012; Tucker and Stern, 2011). More recent analysis of the reserve theory by Stern and Barulli (2019) has shown that CR and BR are interrelated, and differentiating between these two types of reserve has become increasingly difficult. Therefore, we will refer to the concept of CR and BR as *reserve* for the remainder of our review.

Previous studies have shown that the pathologic process of neurodegenerative diseases, such as Alzheimer and Parkinson, may begin before signs of cognitive impairment are apparent (Foster et al, 2010; Morris, 2005) or simultaneously with subtle cognitive deficits that are difficult to detect (Bosboom et al, 2004). Cognitive deficits have also been well studied in individuals with structural neurologic diseases, such as brain tumors and traumatic

brain injury (TBI), with these individuals demonstrating problems specifically with attention, memory, and executive functioning (Benedictus et al, 2010; Nicholl and LaFrance, 2009; Tucha et al, 2000). Not only were these deficits apparent at the time of diagnosis, but they were also apparent several years after treatment intervention and recovery (Lawrie et al, 2019; Ruttan et al, 2008).

A systematic review of the effects of reserve on individuals with these diseases has not yet been published. Understanding cognitive impairments in relation to reserve in a variety of neurodegenerative and structural diseases and malignancies may provide further insight into reserve's role during the course of a disease and recovery. We aimed to systematically review the effects of reserve on cognitive outcomes, including attention, memory, executive functioning, and processing speed, in adult individuals with neurodegenerative and structural CNS diseases.

METHOD

We searched PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsychInfo on October 9, 2019, for relevant published studies on the effects of CR on individuals with a CNS disease using the search terms ("Cognitive Reserve"[MeSH Major Topic] OR "Cognitive Reserve"[Title/Abstract]) AND ("Central Nervous System Diseases"[MeSH Major Topic] OR "CNS diseases"[Title/Abstract] OR "brain injuries"[Title/Abstract]) Filters: English; Adult 19 years+. Our search included published, English-language, peer-reviewed, quantitative, qualitative, or mixed methods studies with no publication year limitations. The database search retrieved 113 citations from PubMed, 45 citations from CINAHL, and one citation from PsychInfo. Two authors (V.R.J. and D.C.) performed the initial search and screened 159 titles and abstracts, and two authors (V.R.J. and T.S.A.) reviewed 19 eligible full-text articles based on our inclusion and exclusion criteria.

Eligibility Criteria and Study Selection

On July 9, 2020, we conducted a secondary search using the same criteria, which yielded two additional published papers that we added to the review. Figure 1 shows the final selection process of these references, resulting in 17 studies meeting all of the criteria for inclusion. Studies were included in our review based on the following criteria:

- English language quantitative, qualitative, or mixed-methods studies;
- Adult participants (19+ years);
- Used CR measures;
- Used neuropsychological testing with or without brain imaging analyses as a measure of cognitive outcomes; and
- Participants were diagnosed with either Alzheimer disease (AD), Parkinson disease (PD), TBI, frontal lobe disease, or lesions.

Studies that were not written in English, that included pediatric patients, and that did not include neuropsychological testing or brain imaging were excluded from our review.

Assessment of Bias

We assessed each study's risk of bias based on items from the Cochrane Collaboration Risk of Bias tool and modified criteria outlined by Tooth et al (2005), which was further modified by Kohler et al (2020). Our assessment included study selection and reporting of findings. V.R.J. and T.S.A. completed this process.

RESULTS

There were 17 studies of reserve in individuals with the selected CNS diseases, for a total of 13,162 individuals, with 87% of the study individuals having AD. The majority of the studies evaluated the role of reserve on cognitive outcomes of individuals with a CNS disease. One paper evaluated the role of reserve in individuals with a brain tumor. In all of the studies, reserve was defined as premorbid factors that explain discrepancies between the degree of neuropathological changes and the disease's clinical presentations. Reserve was not measured consistently across studies; however, one's level of education was the most commonly used measure of reserve. Table 1 outlines details of the population studied, primary objective, study design, and key findings of each study.

Risk of Bias

The risk of bias results for all of the studies are provided in Table 2. Based on our risk of bias assessment, all 17 studies included in our review were considered to be high risk as a result of convenience sampling. Of these, four studies (24%) included a control group that was screened using the same diagnostic criteria as those used with the disease group. Only seven studies (41%) evaluated a history of psychiatric disorders as a part of the exclusion criteria for the study. All of the studies included cognitive outcome measures that are valid and reliable.

Studies Focusing on Individuals With PD

Four studies including a total of 658 individuals reported on the relationship between reserve (as measured by education level) and cognitive outcomes in individuals with PD (Ciccarelli et al, 2018; Guzzetti et al, 2019; Hindle et al, 2016; Koerts et al, 2013), with the study by Hindle et al (2016) enrolling the majority (80%) of individuals. All of the studies included a sample of mostly male individuals and reported significant associations between reserve and cognitive outcomes in a range of domains, such as memory, language, and executive functioning. None of the studies included brain imaging as an additional measure of reserve.

Three studies were exclusively cross-sectional analyses, and only one had a longitudinal component (Hindle et al, 2016), which measured reserve at a baseline time point and at a 4-year follow-up. All of the cross-sectional studies reported that higher reserve was associated with better performance on cognitive outcomes, including memory (Guzzetti et al, 2019; Koerts et al, 2013), executive functioning (Guzzetti et al, 2019; Koerts et al, 2013), working memory (Ciccarelli et al, 2018), verbal fluency (Ciccarelli et al, 2018; Hindle et al, 2016), and visuospatial function (Hindle et al, 2016). However, reserve and

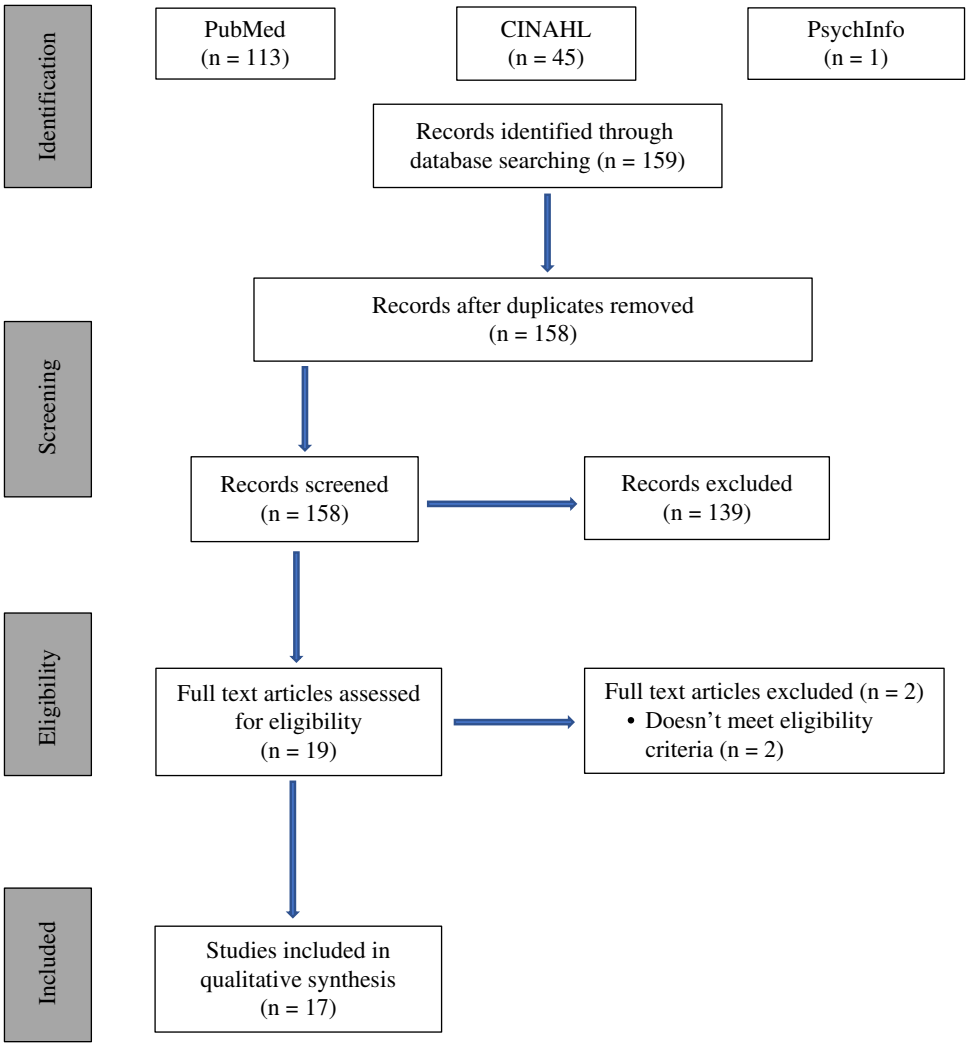

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of our systemic review on the effects of cognitive reserve on functional outcomes of CNS diseases.

cognitive outcomes were not measured similarly across the studies.

Hindle and colleagues (2016) showed no association between reserve and cognitive outcomes at follow-up, despite an association at the baseline measurement. Considered in total, evaluating individuals with PD over time and with a longer follow-up period may provide different results for cognitive outcomes that would be influenced by disease progression and variable rates of functional decline. Therefore, longer term assessments are important in providing a greater understanding of the effects of reserve on disease outcomes in general.

Studies Focusing on Individuals With AD

Four studies including a total of 11,495 individuals, including those with disease or preclinical AD, reported on the relationship between reserve and its outcomes in individuals with AD (Groot et al, 2018; Kadlec et al, 2018; Negash et al, 2013; Soldan et al, 2017), with the study by Kadlec et al (2018) enrolling the majority (91%) of individuals. All four studies included a sample of mostly female individuals. Education level and/or National Adult Reading Test score (Spreen and Strauss, 1998) was used as a measure of reserve. Two of the studies included the measure of intracranial volume as a measure of reserve in addition to education level, while also comparing the effects of reserve in individuals with AD to those who are considered resilient or are in the predementia stage of AD based on pathology (Groot et al, 2018; Negash et al, 2013). However, cognitive outcomes were not measured consistently across the studies, with the study by Kadlec and colleagues (2018) assessing global cognition and the others assessing specific cognitive domains of memory, attention, executive functioning, and visuospatial function (Groot et al, 2018; Negash et al, 2013; Soldan et al, 2017). The study by Soldan et al (2017) included only individuals who presented with preclinical AD, as determined by biomarkers, and reported the longitudinal effects of reserve during disease progression.

TABLE 1. Review of Cognitive Reserve Studies

Reference	Population & Sample	Primary Objective	Study Design & Instruments	Key Findings & Limitations
Ciccarelli et al (2018)	35 participants M age = 76 77% male Individuals with PD without dementia Italy	To investigate how CR influences cognitive performance in participants with PD without dementia	**Design:** cross-sectional CR measurement: CRI (Nucci et al, 2012) (education, working activity, and leisure time) and Brief Intelligence Test (Kaufman and Kaufman, 2004) Verbal long-term memory: RAVLT (Spreen and Strauss, 1998) Verbal working memory: DSF (Monaco et al, 2013) Reasoning: Raven's Matrices (Raven and Raven, 2003) Executive function: Word Fluency (Tombaugh et al, 1999), DSB (Monaco et al, 2013), Rey-Osterrieth figure copy (Spreen and Strauss, 1998), Double Barrage (Saikaley et al, 2018)	**Findings:** CR showed significant associations with Word Fluency and DSB. Higher CRI independently predicted better word fluency. Brief Intelligence Test predicted better DSB scores. No association between CRI and other cognitive domains except reasoning **Limitations:** Small sample size
Dodich et al (2018)	37 participants M age = 69 years 70% male Individuals with behavioral variant frontotemporal dementia Italy	To investigate the effect of occupation on brain functional reserve in participants with behavioral variant frontotemporal dementia	**Design:** cross-sectional CR measurement: occupation profiles BR measurement: glucose hypometabolism in the dorsolateral prefrontal cortex Neuropsychological tests: Phonemic and Semantic Fluency (Tombaugh et al, 1999), Attention Matrices (Scarpa et al, 2006), DSF, RAVLT (Spreen and Strauss, 1998), Rey-Osterrieth Complex Figure (Spreen and Strauss, 1998), Raven's Progressive Matrices (Raven and Raven, 2003), Token Test (Spreen and Strauss, 1998) Global cognition: MMSE (Crum et al, 1993)	**Findings:** Positive association between occupation levels and glucose hypometabolism Jobs requiring more social networking, job context adaptation, and cognitive control showed more severe hypometabolism. Jobs requiring high social interactions, attention, and executive skills may promote support of cognitive function in neurodegenerative processes. **Limitations:** Small sample size Did not use brain structure volumes for BR
Donders and Stout (2019)	121 participants M age = 41 years 59% male Individuals diagnosed with uncomplicated mild TBI (n = 75) and complicated mild to severe TBI (n = 46) Assessed within 1–12 months post injury United States	To determine the protective role of CR in relation to psychometric intelligence after TBI	**Design:** cross-sectional CR measurement: Test of Premorbid Functioning (Holdnack et al, 2013) and demographics Verbal comprehension, perceptual reasoning, working memory, and processing speed: WAIS–IV (Wechsler, 2008)	**Findings:** High CR was associated with better scores on the WAIS–IV in all four domains. Injury severity was a significant predictor for processing speed. **Limitations:** No inclusion of individuals who were several years post injury No inclusion of premorbid brain volumes or leisure activities in the measurement of CR
Groot et al (2018)	663 participants M age = 66 years 49% male Individuals who were AD biomarker-positive with dementia (n = 462) or in predementia stages (n = 201) Amsterdam	To examine cross-sectional effects of CR and BR on cognition in participants with AD	**Design:** cross-sectional CR measurement: education BR measurement: intracranial volume Memory: visual association test, RAVLT Attention: DSF, TMT Part A (Lezak et al, 2004), Stroop I and II (Stroop, 1935) Executive functioning: FAB (Apollonio et al, 2005), Stroop Form III (Stroop, 1935), DSB	**Findings:** CR and BR have positive effects on all cognitive domains. The effects of CR on attention and executive functioning were greater for participants in the predementia stages than participants with dementia. The effects of CR were greater than the effects of BR.

			Language: Category Fluency Test (Tombaugh et al, 1999), naming of visual association test (Lindeboom et al, 2002) Visuospatial: Number Location, Dot Counting, and Fragmented Letters (Spreen and Strauss, 1998) Global cognition: MMSE	**Limitations:** Only used education as a proxy for CR
Guzzetti et al (2019)	50 participants Ages 35–89 years (M = 70) 72% male Individuals diagnosed with PD Grouped by low disease duration (1–9 years) and medium to high disease duration (>9 years) Italy	To evaluate the association of CR with cognition and motor functions of participants with PD at different stages of disease	**Design:** cross-sectional CR measurement: CRI Cognitive impairment screening: MMSE Visual constructive functioning: Clock Drawing Test (Shulman, 2000) Memory: RAVLT, DSF, Corsi Span Forward (Monaco et al, 2013) Executive functioning: FAB, WAIS–R Similarities subtest (Wechsler, 1981), Phonemic Fluency Abstract/logical reasoning: RCPM (Raven and Raven, 2003) Language: Semantic Fluency Test	**Findings:** Supported previous findings of cognitive dysfunction in increased disease duration. Higher CR showed reduced motor impairment and high cognitive functioning. Short-term memory and executive functioning were affected. Protective role of CR was larger in the medium to high disease duration group. Only CRI score had a relationship with disease duration. Education showed no relationship with disease duration. **Limitations:** Small sample size
Hindle et al (2016)	525 participants Ages 32–94 years (M = 68) 65% male Individuals with PD 195 participants were lost to follow-up United Kingdom	To examine the effects of CR on cognition and cognitive decline in individuals with PD	**Design:** cross-sectional and longitudinal analyses (4-year follow-up) CR measurement: education, socio-occupational status, current social engagement Cognitive outcomes: MMSE, ACE–R (Mioshi et al, 2006), Clinical Dementia Rating (Morris, 1993)	**Findings:** At baseline, high education level, social class, and telephone use was associated with higher scores on cognitive outcome assessments. At follow-up, there was no significant association between cognitive scores in year 4 and CR proxies. **Limitations:** Only 4-year follow-up—may show different results if looked at more long-term
Kadlec et al (2018)	10,475 participants M age = 80 40% male Individuals with AD and related dementias Not placed in residential care before initial assessment Assessed from 0–30 months before residential care placement Canada	To examine how cognitive functioning in AD and related dementias changes over time and its relationship to education levels and the relationship between SMMSE (Molloy and Standish, 1997) scores and education level	**Design:** longitudinal (6- to 12-months follow-up) CR measurement: education levels Cognitive functioning: SMMSE	**Findings:** High education levels were associated with higher SMMSE scores. Individuals with higher education levels showed faster decline in cognitive functioning as they got closer to residential care placement (end of disease progression). **Limitations:** Only used education as a proxy for CR
Koerts et al (2013)	48 participants M age = 63 58% male	To determine to what extent CR influences cognition	**Design:** cross-sectional CR measurement: NART (Spreen and Strauss, 1998) and education level	**Findings:** Age, gender, and depression were not independent predictors of cognition.

TABLE 1. (*continued*)

Reference	Population & Sample	Primary Objective	Study Design & Instruments	Key Findings & Limitations
	Individuals with PD The Netherlands	in participants with PD	Executive function: Stroop, TMT, DSB, Semantic and Phonemic Fluency Memory: RAVLT, DSF Psychomotor speed: TMT Part A, Stroop Word Card	NART score was an independent predictor of executive functioning, memory, and psychomotor speed. Education was highly correlated with NART score but was not a predictor of cognition. **Limitations:** Did not include other measures of CR such as occupation
Krch et al (2019)	61 participants Ages 18–65 years (M = 41) 75% male Individuals with complicated mild to severe TBI ≥1 year post injury United States	To verify cognitive evidence of CR in individuals with TBI and to extend prior research by investigating CR's moderating effects	**Design:** cross-sectional CR measurement: WTAR (Wechsler, 2001) BR measurement: white matter integrity Noncontextualized memory: CVLT–II (Delis et al, 2000), WMS–IV Designs 1 and 2 (Holdnack et al, 2013), BVMT (Spreen and Strauss, 1998) Contextualized memory: WMS–IV Logical Memory I and II (Wechsler, 2009) Attention: DSF, Brief Test of Attention (Spreen and Strauss, 1998) Executive function: Stroop–Color-Word, Color Trails Test 2 (Spreen and Strauss, 1998), Phonemic and Semantic Fluency Processing speed: Symbol Digit Modalities (Smith, 1982), WAIS–IV Symbol Search, Color Trails Test 1, Letter and Pattern Comparison (Salthouse and Babcock, 1991), Stroop Color Naming, and Word Reading (Wechsler, 2008)	**Findings:** The high CR group performed significantly better than the low CR group in contextualized memory and executive function. The high CR and low CR groups performed similarly on processing speed. Significant interactions were found between WTAR score and white matter integrity for both memory domains. Higher CR had a protective effect on memory and executive functioning. No significant interactions for other domains **Limitations:** Small sample size No baseline measurement of CR or baseline neuropsychological testing for comparison
Leary et al (2018)	100 participants Average age = 47 63% male Individuals with mild TBI (n = 58), moderate TBI (n = 25), and severe TBI (n = 17) ≥1 year post injury United States	To investigate the relation between factors of CR and post TBI neuropsychological and functional outcomes	**Design:** cross-sectional CR measurement: Test of Premorbid Functioning and demographics Neuropsychological tests: Booklet Category Test (DeFilippis and McCampbell, 1997), CVLT–II, Finger Tapping Test (Spreen and Strauss, 1998), PEG (Spreen and Strauss, 1998), TMT, WAIS–IV Functional outcomes: Glasgow Outcome Scale-Extended (McMillan et al, 2016), Short Form-36 Health Survey (Jenkinson et al, 1993)	**Findings:** Strong CR resulted in better neuropsychological outcomes. Occupational attainment did not correlate with neuropsychological or functional outcomes. Functional outcomes were not related to factors of CR. **Limitations:** Participants all had above-average education levels. Did not consider effects of cognitive rehabilitation post injury Did not include premorbid participation in cognitively stimulating activities
Macpherson et al (2017)	228 participants M age = 46 years Individuals with lesion to frontal region from stroke	To investigate the independent effects of education and NART IQ on	**Design:** cross-sectional CR measurement: education and NART IQ score Neuropsychological tests: Phonemic Fluency,	**Findings:** NART score predicted executive and naming performance. Education and NART score

	(n = 22) or brain tumor (n = 64) and HC (n = 142) United Kingdom	cognitive outcomes in participants with focal, unilateral frontal lesions	Stroop, RAPM, TMT, Digit Span, Graded Naming Test (McKenna and Warrington, 1983), Object Decision Test (Warrington and James, 1991)	contributed to naming performance, but education was not independent of NART score. Both education and NART score were not predictive of performance on fluid intelligence, processing speed, verbal short-term memory, or perceptual abilities. **Limitations:** Did not examine effects of CR on cognition over time Lesion resection occurred before neuropsychological testing. Cognitive outcomes of surgery may play a role in performance on tests. Participants with lesions from a stroke were not excluded. Differences in neuropathology between stroke and brain tumor may contribute to different results.
Negash et al (2013)	54 participants M age = 73 years 43% male Individuals with AD dementia (n = 36) and with resilience to AD dementia based on pathology (n = 18) Resilience indicated the individual was in a prodromal phase of neurodegeneration United States	To test proxies of CR and BR and determine their association with cognitive function in AD pathology	**Design:** cross-sectional CR measurement: education level BR measurement: intracranial volume Neuropsychological tests: Word List, Clock Drawing, Category Fluency, Boston Naming Test (Kaplan et al, 1983), Praxis Construction (Spreen and Strauss, 1998), Digit Symbol (Wechsler, 2008), Logical Memory (Wechsler, 2009)	**Findings:** The resilient group had more education and a larger intracranial volume than the group with AD dementia. Larger cranial size was associated with resilience in the absence of education. **Limitations:** Small sample size
Oldenburg et al (2016)	122 participants Age = 15–65 years (M = 37) 57% male Individuals with mild TBI assessed at baseline within 24 hours after trauma HC (n = 35) recruited at follow-up Sweden	To investigate the association between cognitive performance and postconcussion symptoms in relation to CR	**Design:** longitudinal (3-month follow-up) CR measurement: WAIS–R, education level, and occupational skill level Outcome measures: RPQ (King et al, 1995), PASAT (Spreen and Strauss, 1998), Selective Reminding Test (Spreen and Strauss, 1998), Stroop, Digit Span, Digit Symbol, TMT, Reliable Digit Span (Greiffenstein et al, 1994)	**Findings:** Participants with mild TBI performed worse on the Selective Reminding Test than participants who had recovered from a mild TBI. Inverted relationship between all three measures of CR and postconcussion symptoms **Limitations:** High rate of decline for participation Dropouts had fewer years of education. HC included participants with no injury in general rather than participants with no brain injury.
Placek et al (2016)	145 participants M age = 61 years 59% male Individuals diagnosed with	To evaluate if CR contributes to differences in frontal gray matter	**Design:** cross-sectional CR measurement: composite of education and occupation BR measurement: gray matter density	**Findings:** Higher CR was associated with better performance on Letter Fluency. Higher CR was not associated with MMSE,

TABLE 1. (*continued*)

Reference	Population & Sample	Primary Objective	Study Design & Instruments	Key Findings & Limitations
	frontotemporal lobar degeneration (n = 55) and demographically matched HC (n = 90) United States	density and executive impairment in the disease course of frontotemporal lobar degeneration	Neuropsychological tests: Letter Fluency, MMSE, DSF, Rey Figure Copy, Boston Naming Test	DSF, Rey Figure Copy, or Boston Naming Test. Higher CR was associated with greater gray matter density in the right frontal cortex CR in the HC was only related to a higher gray matter density in the left inferior frontal gyrus. **Limitations:** Tests performed at variable time points of disease progression
Sandry et al (2015)	50 participants Average age = 38 years 74% male Individuals with moderate to severe TBI ≥1 year post injury United States	To investigate the link between CR and long-term memory impairment due to TBI	**Design:** cross-sectional CR measurement: WTAR Verbal memory: CVLT–II, Prose Memory of the Memory Assessment Scale (Williams et al, 1991) Working memory: Digit Span, Letter Number Sequencing (Wechsler, 2008)	**Findings:** Working memory capacity partially mediates the relationship between CR and long-term memory in individuals with TBI. Significant correlation between CR and working memory, working memory and long-term memory, and CR and long-term memory **Limitations:** Small sample size
Soldan et al (2017)	303 participants M age = 57 years 42% male Individuals with AD biomarkers United States	To examine the association between CR, biomarker levels of AD, and the long-term cognitive trajectories	**Design:** cross-sectional and longitudinal analyses (up to 20-year follow-up) CR measurement: composite of NART, vocabulary subscore on WAIS (Wechsler, 1981), and education Neuropsychological tests: Paired Associates Immediate (Wechsler, 1997), Logical Memory Delayed (Wechsler, 2009), Boston Naming Test, Digit Symbol	**Findings:** Individuals who remained cognitively normal and had a lower biomarker composite showed a positive association between CR and cognitive performance. CR had no impact on the rate of change in cognition. Participants who progressed to MCI and had high biomarker scores reported a positive association between CR and baseline cognitive performance. High CR was associated with a fast rate of cognitive decline after onset of MCI symptoms. Participants who progressed to MCI had lower baseline CR scores. Higher CR scores were strongly associated with an older age of symptom onset. **Limitations:** Did not include participants with clinical symptoms of AD at baseline
Steward et al (2018)	175 participants Age = 19–79 years (M = 35) 61% male Individuals with TBI (n = 109) and demographically	To assess whether CR predicts cognitive outcomes post TBI and the rate of recovery	**Design:** longitudinal (1-, 6-, and 12-month follow-up) CR measurement: WTAR Processing speed: TMT, Digit Symbol Coding and Symbol Search Verbal fluency: Animal Fluency, Fruit/Vegetable Fluency, Clothing Fluency (Spreen and Strauss, 1998)	**Findings:** Higher CR was associated with better cognitive outcomes in all three domains. No evidence of interaction between CR and TBI severity No evidence of brain damage threshold for effectiveness of CR

matched controls (n = 66)	Memory: CVLT–II, Logical Memory I and II (Wechsler, 2009)	**Limitations:** Unable to separate moderate TBI from severe TBI during analyses
Assessed within 2–6 weeks post injury and at 6 and 12 months post injury		Did not have a true measure of premorbid IQ
United States		

Complete references for all tests are provided in the References section.
ACE–R = Addenbrooke's Cognitive Examination Revised. **AD** = Alzheimer disease. **BR** = brain reserve. **BVMT** = Brief Visuospatial Memory Test. **CR** = cognitive reserve. **CRI** = Cognitive Reserve Index. **CVLT** = California Verbal Learning Test. **DSB** = Digit Span Backward. **DSF** = Digit Span Forward. **MCI** = mild cognitive impairment. **FAB** = Frontal Assessment Battery. **HC** = healthy controls. **MCI** = mild cognitive impairment. **MMSE** = Mini-Mental State Examination. **NART** = National Adult Reading Test. **PASAT** = Paced Auditory Serial Addition Test. **PD** = Parkinson disease. **PEG** = Grooved Pegboard Test. **RAPM** = Raven's Advanced Progressive Matrices. **RAVLT** = Rey Auditory Verbal Learning Test. **RCPM** = Raven's Coloured Progressive Matrices. **RPQ** = Rivermead Post Concussion Symptoms Questionnaire. **SMMSE** = Standardized Mini-Mental State Examination. **TBI** = traumatic brain injury. **TMT** = Trail Making Test. **WAIS** = Wechsler Adult Intelligence Scale. **WMS** = Wechsler Memory Scale. **WTAR** = Wechsler Test of Adult Reading.

When analyzed cross-sectionally and comparing groups based on their level of dementia from disease progression, all of the studies reported a positive association between reserve and cognitive outcomes. Both of the longitudinal studies unexpectedly found that individuals with a high reserve showed faster decline in cognitive functioning as the disease progressed compared with those with a low reserve (Kadlec et al, 2018; Soldan et al, 2017).

Intracranial volume had positive effects on cognitive outcomes in both studies in which it was measured (Groot et al, 2018; Negash et al, 2013). In the absence of high education, a larger intracranial volume was associated with resilience in individuals with AD, indicating that intracranial volume has independent effects on cognition (Negash et al, 2013). However, the study by Groot et al (2018) reported that the effects of education level were stronger than the effects of intracranial volume. In total, these four studies suggest that a more comprehensive index, such as the use of both education status and brain volume, as a measure of reserve may provide a better predictor of disease impact on long-term cognitive function.

Studies Focusing on Individuals With TBI

Six studies including a total of 629 individuals reported on the relationship between reserve and cognitive outcomes in individuals with TBI, with all of the studies including a sample of mostly male individuals (Donders and Stout, 2019; Krch et al, 2019; Leary et al, 2018; Oldenburg et al, 2016; Sandry et al, 2015; Steward et al, 2018). The individuals in three of the studies completed testing on cognitive outcomes at least 1 year post injury (Krch et al, 2019; Leary et al, 2018; Sandry et al, 2015), whereas the individuals in the other three studies completed testing within a 1-year period (Donders and Stout, 2019; Oldenburg et al, 2016; Steward et al, 2018).

As with the studies of other CNS diseases, reserve and cognitive outcomes were not measured consistently. Reserve was measured using the Wechsler Test of Adult Reading (Wechsler, 2001) in three of the studies (Krch et al, 2019; Sandry et al, 2015; Steward et al, 2018), only the Test of Premorbid Functioning (Holdnack et al, 2013) in Donders and Stout (2019), and education level and occupational skill level in addition to premorbid IQ estimate in the remaining two studies (Leary et al, 2018; Oldenburg et al, 2016). No studies used brain imaging as a measure of reserve. Two of the studies included demographically matched healthy controls in their analysis of reserve's role in individuals with TBI (Oldenburg et al, 2016; Steward et al, 2018).

Overall, five of the six studies found a positive correlation between reserve and cognitive outcomes in different cognitive domains (Donders and Stout, 2019; Krch et al, 2019; Leary et al, 2018; Sandry et al, 2015; Steward et al, 2018). The study by Oldenburg et al (2016) used three measures of reserve (premorbid IQ, education level, and occupational skill level) and tested cognitive outcomes at 3 months post injury. They reported that all three measures showed an inverse relationship with

TABLE 2. Risk of Bias Assessment

	Ciccarelli et al (2018)	Dodich et al (2018)	Donders and Stout (2019)	Groot et al (2018)	Guzzetti et al (2019)	Hindle et al (2016)	Kadlec et al (2018)	Koerts et al (2013)	Krch et al (2019)	Leary et al (2018)	Macpherson et al (2017)	Negash et al (2013)	Oldenburg et al (2016)	Placek et al (2016)	Sandry et al (2015)	Soldan et al (2017)	Steward et al (2018)
Cases are representative	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Initial numbers accounted for	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Appropriate diagnostic criteria	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Controls screened using same diagnostic criteria	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	+	+	+	+	NA	NA	+
Screening for psychiatric disorders	+	–	+	+	–	–	–	–	+	–	+	–	+	–	–	–	+
Outcome assessors blinded to group status	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	–	–	–	–	NA	NA	–
Controlled for cofounding variables	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Appropriate subgroup evaluation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Missing data	–	–	+	+	+	+	+	–	–	+	+	+	+	–	–	+	+
Appropriate methods to deal with missing data	NA	NA	+	+	+	+	+	NA	NA	+	+	+	+	NA	NA	+	+
All outcomes and groups reported	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Valid cognitive measures	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Reliable cognitive measures	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ = yes. – = no. **NA** = not applicable.

postconcussion symptoms, and individuals with these symptoms consistently reported lower mean scores on neuropsychological tests of executive functioning, memory and learning, attention, and processing speed than healthy controls or individuals who did not have postconcussion symptoms (Oldenburg et al, 2016). However, the rate of cognitive decline for individuals in this study was high, which may have exaggerated any differences between the groups.

Some of the studies had significant limitations in terms of generalizability, including one that included a population that had a higher than average education level (Leary et al, 2018) and three that lacked a control group or baseline neuropsychological testing before TBI to compare cognitive outcomes (Donders and Stout, 2019; Krch et al, 2019; Sandry et al, 2015). Baseline testing scores or control groups in the studies may have led to more accurate differences in outcome measures.

Studies Focusing on Individuals With Frontal Lobe Disease

Two studies including a total of 182 individuals reported on the relationship between reserve and cognitive outcomes in individuals with frontal lobe disease (Dodich et al, 2018; Placek et al, 2016), with the study by Placek et al (2016) enrolling the majority (80%) of individuals, who had been diagnosed with frontotemporal lobar degeneration. In both of the studies, reserve was measured differently, whereas the cognitive outcomes were measured similarly through neuropsychological testing, with the study by Placek and colleagues (2016) including gray matter density as an outcome measure.

Both studies used different neuropsychological tests, except for short-term memory, but similar overall cognitive domains were measured. The study by Dodich et al (2018) used occupation profiles and glucose hypometabolism, which is known to have a positive association with reserve, as a measure of reserve, and the study by Placek and colleagues (2016) used a composite of education and occupation levels and gray matter density as a measure of reserve. Both studies reported a positive association between reserve and cognitive outcomes as measured by neuropsychological test scores. The study by Placek and colleagues (2016) included demographically matched healthy controls and showed that although high reserve was associated with better performance on letter fluency, it was not associated with better performance on attention, visuospatial function, global cognitive impairment, or language. These two studies were limited in that the timing of assessment in relation to disease duration was variable, as was the timing of the various tests.

Studies Focusing on Individuals With Focal Frontal Lesions

One study including a total of 228 individuals, 62% of whom were demographically matched healthy controls, reported on the relationship between reserve and cognitive outcomes in individuals with focal, unilateral frontal lesions (Macpherson et al, 2017). Individuals who were enrolled in this study included those who had a lesion from a stroke or a brain tumor. Reserve was measured by education level and the National Adult Reading Test; cognitive outcomes were measured through various neuropsychological tests. National Adult Reading Test scores were found to be predictive of executive functioning and naming performance. Education was not an independent predictor of cognitive outcomes and was predictive of naming performance only in the presence of National Adult Reading Test scores. Lesion resection occurred before all neuropsychological testing, and the cognitive outcomes from surgery independent of the disease may have affected the individuals' performance on the assessments.

This study did not assess the effects of reserve longitudinally, which may have provided more information on reserve's role in disease progression in this population. In addition, the differences in neuropathology between a lesion resulting from a stroke and a lesion resulting from a brain tumor may have had underlying effects on the individuals' cognition. Including an analysis of lesion location (left vs right brain) with respect to reserve would have provided further insight into its effects on cognitive outcomes.

DISCUSSION

Our systematic review included 17 studies on the role of reserve on functional outcomes associated with cognition in individuals with CNS diseases. The studies involved various measures of reserve, with education level being the most common. Some of the studies included the use of brain imaging as a measure of reserve; all of the studies used neuropsychological testing as a measure of cognition. Nearly all of the studies, regardless of CNS disease or injury diagnosis, reported a positive association between reserve and neuropsychological testing scores when studied cross sectionally. When studied longitudinally, reserve either showed no effects on, or correlated to a faster decline in, cognition at disease progression (Hindle et al, 2016; Kadlec et al, 2018; Soldan et al, 2017). An understanding of reserve in neurologic diseases may help us to better understand potential predictors of disease outcomes and create more targeted evaluation and cognitive treatment methods.

The majority of individuals in the studies we reviewed had AD, with the study by Kadlec and colleagues (2018) consisting of 10,475 individuals. This study used only education level as a measure of reserve rather than a combination of education level, occupational skill level, and intracranial volume. In addition, only the Standardized Mini-Mental State Examination (Molloy and Standish, 1997) was used as a measure of cognition in this study, rather than more comprehensive neuropsychological tests that would indicate the function of more specific cognitive domains. Therefore, the results of the review of individuals with AD may be skewed, and more studies looking at reserve in individuals with AD should include a combination of measures of reserve and more tools to measure cognitive outcomes.

The studies of individuals with TBI showed a lack of generalizability due to a higher than average education

level among the individuals in one study (Leary et al, 2018) and a lack of baseline neuropsychological testing scores or a control group in the other three studies (Donders and Stout, 2019; Krch et al, 2019; Sandry et al, 2015). Many of the studies in our review showed the need for assessing cognitive outcomes associated with reserve in a longitudinal perspective. In the studies on individuals with PD, disease progression may cause a decline in cognitive outcomes, which may not be accounted for when those individuals are studied cross sectionally. The long-term effects of reserve in individuals with frontal lobe disease can also provide more insight into how disease progression may affect the outcomes observed because the studies that were included had individuals at variable times of disease duration (Dodich et al, 2018; Placek et al, 2016).

Even though a positive association was found between reserve and cognitive outcomes at baseline, the longitudinal study on PD showed that this association did not exist at a 4-year follow-up period (Hindle et al, 2016). The large study on individuals with AD and the study on individuals with preclinical AD showed that, when looked at longitudinally, those with a high reserve declined in cognitive function faster than those with a low reserve (Kadlec et al, 2018; Soldan et al, 2017). The differences in results of these three studies compared with the results of the other studies in this review clearly indicate the need for more longitudinal studies to create a more accurate and reliable picture of the effects of reserve over time.

The one study involving individuals with a brain tumor also included individuals with lesions resulting from a stroke (Macpherson et al, 2017). Differences in neuropathology and the onset of symptoms between these two diagnoses may have had an impact on the relationships reported. Neuropsychological testing was done after lesion resection, indicating that the performance on these tests may have been affected by surgery and independent of the disease. Lastly, performing studies on the effects of reserve over time and during disease progression is necessary because the lack of a longitudinal analysis in this study limits the understanding of reserve's role in the population with a brain tumor.

Limitations

It is possible that limiting our search to English-language publications and using the search term "central nervous system diseases" rather than the names of the diseases themselves may have resulted in the unintended exclusion of relevant literature. Nevertheless, our findings are compelling and underscore the need for additional research in this area.

CONCLUSION

While almost all of the studies that we reviewed showed that a greater reserve is associated with better cognitive outcomes across the neurologic disorders studied, these studies were limited by their cross-sectional design. Further studies assessing the effects of reserve longitudinally across all of these populations are needed in order to predict the outcomes more accurately. With these caveats in mind, the findings from our systematic review suggest that reserve may serve as a predictor for cognitive outcomes in individuals with a CNS disease.

The positive association between education level (the most common measure of reserve in our review) and cognitive function suggests a need to implement societal policies to improve education, and in turn, health outcomes. The World Health Organization (2021) has recognized education as a social determinant of health, and studies have reported on the positive association between education attainment and health (Goldman and Smith, 2011; Masters et al, 2012). Our findings suggest that implementing systems that address both health and access to quality education in the early years of life may improve cognitive outcomes during the course of the disease and recovery.

The results of our review also highlight the importance of evaluating impact longitudinally and the need to develop a standardized multifaceted approach that includes functional measures along with demographics such as education level and occupational skill level. These metrics and the collection of data longitudinally are necessary to understand and advance the concept of reserve in CNS disease; they also have implications for the evaluation and timing of interventions to preserve function or facilitate coping. A better understanding of the prognosis of disease in terms of cognition may allow clinicians to understand and mitigate risk and to plan and create more targeted treatment methods, potentially resulting in improved cognitive outcomes for individuals.

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